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EXAMINER	
HENRY, MICHAEL C	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/501,030	FUSENIG ET AL.	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-27 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-27 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following office action is a responsive to the Amendment filed, 10/01/08.

The amendment filed 10/01/08 affects the application, 10/501,030 as follows:

1. Claim 1 has been amended. Claim 28 has been canceled. New Claims 31-35 have been added. The rejections of the prior office action made under 35 U.S.C. 103(a) and mailed on 04/01/08 are maintained.
2. The responsive to applicants' amendments and arguments is contained herein below.

Claims 18-27 and 30-35 are pending in the application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-27 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willoughby et al. (WO 94/23725) in view of Pressato et al. (WO 97/07833).

In claim 18 applicant claims "A method for the treatment and care of primary and secondary tumors by inhibiting angiogenesis which comprises applying at the tumor site a biomaterial comprised of a benzyl ester of hyaluronic acid wherein said hyaluronic acid is at least 85% benzyl esterified, and wherein said biomaterial inhibits angiogenic processes related to vascularization." Claims 18-27 and 30 are drawn to said method wherein said hyaluronic acid is benzyl esterified at specific %, wherein the hyaluronic acid is in association with other natural,

synthetic and/or semisynthetic biopolymers, pharmacologically active substance, specific pharmacological active substance and specific form of application to tumor site.

Willoughby et al. disclose the use of hyaluronic acid, including hyaluronic acid esters for the treatment of tumors by inhibiting or regressing angiogenesis (see claims 48-58; see also claims 24-34). Furthermore, Willoughby et al. disclose that their invention provides a process for the inhibition, control and/or regression of angiogenesis, (for example the inhibition of blood vessel growth to a malignant tumour, cutting off blood vessel growth or development, in to a malignant tumour) in a mammal (for example a human), the process comprising the steps of administering an effective dosage amount of a pharmaceutical composition for the inhibition, control and/or regression of angiogenesis to a site on/in the mammal in need of inhibition, control and/or regression ….. (see page 7, lines 6-32; see also page 6, lines 13-21).

The difference between applicant's claimed method and the method disclosed by Willoughby et al. is that Willoughby et al. do not recite the use of a specific ester (i.e., benzyl ester) of hyaluronic acid but teach that esters of hyaluronic acid can be used.

Pressato et al. disclose a biomaterial comprised of benzyl ester of hyaluronic acid in the form of gels, membranes, woven tissues or meshes and nonwoven tissues that can be used to prevent surgical adhesion (page 5, lines 20-26). This suggests that benzyl ester of hyaluronic acid can be in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to the treated site (page 5, lines 20-26). Furthermore, Pressato et al. disclose that their benzyl ester of hyaluronic acid can be 75-100% esterified (see claim 1). In addition, Pressato et al. disclose that biodegradable and non-biodegradable materials such as polymers in their composition.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Willoughby et al. and Pressato et al., to have used the method of Willoughby et al. to treat tumors by inhibiting angiogenesis with a composition (e.g., a biomaterial) comprising a benzyl ester of hyaluronic acid, since Willoughby et al. suggests that esters of hyaluronic acid can be used by application to the tumor site and Pressato et al. disclose that benzyl ester of hyaluronic acid can be prepared in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to a treated site.

One having ordinary skill in the art would have been motivated in view of Willoughby et al. and Pressato et al., to have used the method of Willoughby et al. to treat tumors by inhibiting angiogenesis with a composition (e.g., a biomaterial) comprising a benzyl ester of hyaluronic acid, since Willoughby et al. suggests that esters of hyaluronic acid can be used by application to the tumor site and Pressato et al. disclose that benzyl ester of hyaluronic acid can be prepared in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to a treated site. It should be noted that it is obvious to further include or use pharmaceutically active substance such as antitumor or cancer drugs to treat said tumors.

Claims 31 is drawn to a method for the treatment and care of primary and secondary tumors by inhibiting angiogenesis which comprises applying at the tumor site a biomaterial consisting essentially of a benzyl ester of hyaluronic acid wherein said hyaluronic acid is at least 85% benzyl esterified, wherein said biomaterial inhibits angiogenic processes related to vascularization and wherein said biomaterial is in the form of at least one member selected from

the group consisting of a non-woven felt, sponge, microsphere, film and membrane. Claims 32-35 are drawn to said method wherein said hyaluronic acid is benzyl esterified at specific % and specific form of application to tumor site.

Willoughby et al. disclose the use of hyaluronic acid, including hyaluronic acid esters for the treatment of tumors by inhibiting or regressing angiogenesis (see claims 48-58; see also claims 24-34). Furthermore, Willoughby et al. disclose that their invention provides a process for the inhibition, control and/or regression of angiogenesis, (for example the inhibition of blood vessel growth to a malignant tumour, cutting off blood vessel growth or development, in to a malignant tumour) in a mammal (for example a human), the process comprising the steps of administering an effective dosage amount of a pharmaceutical composition for the inhibition, control and/or regression of angiogenesis to a site on/in the mammal in need of inhibition, control and/or regression ….. (see page 7, lines 6-32; see also page 6, lines 13-21).

The difference between applicant's claimed method and the method disclosed by Willoughby et al. is that Willoughby et al. do not recite the use of a specific ester (i.e., benzyl ester) of hyaluronic acid but teach that esters of hyaluronic acid can be used.

Pressato et al. disclose a biomaterial comprised of benzyl ester of hyaluronic acid in the form of gels, membranes, woven tissues or meshes and nonwoven tissues that can be used to prevent surgical adhesion (page 5, lines 20-26). This suggests that benzyl ester of hyaluronic acid can be in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to the treated site (page 5, lines 20-26). Furthermore, Pressato et al. disclose that their benzyl ester of hyaluronic acid can be 75-100%

esterified (see claim 1). In addition, Pressato et al. disclose that biodegradable and non-biodegradable materials such as polymers in their composition.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Willoughby et al. and Pressato et al., to have used the method of Willoughby et al. to treat tumors by inhibiting angiogenesis with a composition (e.g., a biomaterial) consisting essentially of a benzyl ester of hyaluronic acid, since Willoughby et al. suggests that esters of hyaluronic acid can be used by application to the tumor site and Pressato et al. disclose that benzyl ester of hyaluronic acid can be prepared in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to a treated site.

One having ordinary skill in the art would have been motivated in view of Willoughby et al. and Pressato et al., to have used the method of Willoughby et al. to treat tumors by inhibiting angiogenesis with a composition (e.g., a biomaterial) consisting essentially of a benzyl ester of hyaluronic acid, since Willoughby et al. suggests that esters of hyaluronic acid can be used by application to the tumor site and Pressato et al. disclose that benzyl ester of hyaluronic acid can be prepared in the form of gels, membranes, woven tissues or meshes and nonwoven tissues (of a biomaterial) that can be administered directly to a treated site. It should be noted that it is obvious to further include or use pharmaceutically active substance such as antitumor or cancer drugs to treat said tumors.

Response to Arguments

Applicant's arguments with respect to claims 18-27 and 30-35 have been considered but are not found convincing.

The applicant argues that *Willoughby et al.* disclose compositions with anti-angiogenic activity comprising hyaluronic acid (HA) or a derivative thereof, and also disclose compositions comprising HA or a derivative thereof in a mixture with a non-steroidal anti-inflammatory drug, such as diclofenac. *Willoughby et al.,* however, do not teach any benzyl esters of hyaluronic acid as in the present invention. However, as set forth in the above rejection, Willoughby et al. disclose that hyaluronic acid esters (which includes benzyl) can be used. In addition, it should be noted that the rejection was made by combining Willoughby et al. and Pressato et al. Furthermore, it should be noted that benzyl esters of hyaluronic acid (also known as HYAFF 11; HYAFF-11; benzyl hyaluronate; hyaluronan benzyl ester; hyaluronan total benzyl ester HYAFF11; Hyaluronic acid, phenylmethyl ester) is a commonly used ester form of hyaluronic acid in the art, especially in the form of a membrane (a biomaterial) composed of benzylester hyaluronic acid that is used in surgical or medical procedures such as those involving cell and tissues (see e.g., Exhibit A: Hollander et al., J Wound Care,1999 Jul; 8(7):351-5; Exhibit B: Lobmann R et al., Journal of Diabetes and its Complications, Volume 17, Number 4, July 2003 , pp. 199-204 and Exhibit C: Hum L R et al., International journal of pharmaceutics, 1994, vol. 111, no3, pp. 295-298).

The applicant argues that First of all, HA contains several esterifiable groups and it can form, for example, alcohol or acid esters, aromatic or aliphatic esters, short or long-chain aliphatic esters, and other types of possible "esters". Nevertheless, *Willoughby et al.* merely generically mentions "esters" of hyaluronic acid without any guidance as to the selection of any particular types or individual "esters". This is not a situation wherein there are a "finite" identifiable number of "predictable" solutions that could provide a reasonable expectation of

success as in rationale (E) of the USPTO obviousness guidelines. In the present case, there are a vast number of possible "esters" of hyaluronic acid and the Examiner has not provided any reasoning as to why one skilled in the art reading *Willoughby et al.* would be lead to particularly utilize benzyl esters of hyaluronic acid as in the present invention. However, as set forth in the above rejection, Willoughby et al. disclose that hyaluronic acid esters (which includes benzyl) can be used. In addition, it should be noted that the rejection was made by combining Willoughby et al. and Pressato et al. Furthermore, it should be noted that benzyl esters of hyaluronic acid (also known as HYAFF 11; HYAFF-11; benzyl hyaluronate; hyaluronan benzyl ester; hyaluronan total benzyl ester HYAFF11; Hyaluronic acid, phenylmethyl ester) is a commonly used ester form of hyaluronic acid in the art, especially in the form of a membrane (a biomaterial) composed of benzylester hyaluronic acid that is used in surgical or medical procedures such as those involving cell and tissues (see e.g., Exhibit A: Hollander et al., J Wound Care,1999 Jul; 8(7):351-5; Exhibit B: Lobmann R et al., Journal of Diabetes and its Complications, Volume 17, Number 4, July 2003 , pp. 199-204 and Exhibit C: Hum L R et al., International journal of pharmaceutics, 1994, vol. 111, no3, pp. 295-298).

The applicant argues that a proper reading of *Willoughby et al.* would actually teach against the prior art combination suggested by the Examiner. *Willoughby et al.* report evidence of anti-angiogenic activity only for HA sodium salt in combination with an anti-inflammatory drug. The results in *Willoughby et al.* show that HA alone does not induce any significant effect on tissue vascularity; whereas the combination of HA-Diclofenac significantly reduces vascularity (see page 17, lines 30-34). With these results, one skilled in the art seeking to provide an alternative method for the treatment of tumors would have focused on the combinations of HA

and the anti-inflammatory agent and would not have sought to modify the HA component, which the test results show was not active. On the contrary however, Willoughby et al. disclose that the hyaluronic acid is therapeutically effective substance or component for inhibiting or treating angiogenesis (see abstract). Consequently, Willoughby does not teach away. It should be noted that a reference is not limited to its working examples, but must be evaluated for what it teaches those of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 U.S.P.Q. 507 (C.C.P.A. 1966). In re Chapman, 357 F.2d 418, 148 U.S.P.Q. 711 (C.C.P.A. 1966).

The applicant argues that test data in *Alam et al.* (Enclosure 1) discusses the same test data as reported in the *Willoughby et al.* reference and *Alam et al.* conclude that HA alone does not have any effect on the examined parameters of vascular density and vascular index. However, the rejections set forth above were not made by applying Alam et al.'s reference.

The applicant argues that experimental results subsequent to the filing of the present application have further buttressed this position. Willhauck et al. (Enclosure 2) report on studies utilizing non-woven tissues of HA benzyl esters. Those experiments demonstrated that non-woven tissues of HA benzyl esters possess an anti-invasive activity towards tumors, because they induce the formation of granulation tissue and of a fibrotic connective tissue wherein myofibrils accumulate (see the abstract), thereby forming connective tissue capable of modulating components of the connective stroma in a way that chemotaxis of tumor cells angiogenesis are blocked (see the discussion, lines 1-9 and 17-22). However, the rejections set forth above were not made by applying Willhauck et al.'s reference but by applying a combination of Willhauck et al. and Pressato et al.

The applicant argues that *Willoughby et al.* teach that the described products are applied to the patient's skin and/or exposed tissue or are administered systemically. The present invention, on the other hand, relates to the use of a biomaterial in the form of a non-woven felt, sponge, microsphere, film or membrane which is applied to the tumor site, and can particularly be administered after surgical removal of a tumor. *Willoughby et al.* simply do not teach or suggest use of the biomaterials of the present invention. It should be noted that the rejections were made by combining Willoughby et al. and Pressato et al. Furthermore, Willoughby et al. disclose the use of hyaluronic acid, including hyaluronic acid esters for the treatment of tumors by inhibiting or regressing angiogenesis (see claims 48-58; see also claims 24-34). Furthermore, Willoughby et al. disclose that their invention provides a process for the inhibition, control and/or regression of angiogenesis, (for example the inhibition of blood vessel growth to a malignant tumour, cutting off blood vessel growth or development, in to a malignant tumour) in a mammal (for example a human), the process comprising the steps of administering an effective dosage amount of a pharmaceutical composition for the inhibition, control and/or regression of angiogenesis to a site on/in the mammal in need of inhibition, control and/or regression ..... (see page 7, lines 6-32; see also page 6, lines 13-21). It should be noted that Willoughby teaching of administering the said hyaluronic acid to inhibit or treat angiogenesis of said tumors encompasses applying the said hyaluronic acid to said tumors as well as any of the common routes of administration. It should be noted that the use of different routes of administration of active ingredients or compositions such as Willoughby et al.'s is common in the art, is well within the purview of a skilled artisan and also depends on factors such as the type and/or severity of the tumor, disease or disorders and the type, weight and age of individual treated.

The applicant argues that *Willoughby et al.* teach that HA alone is not active for anti-angiogenic activity, so one skilled in the art would not be lead to select HA benzyl esters for this purpose. On the contrary however, Willoughby et al. disclose that the hyaluronic acid is therapeutically effective substance or component for inhibiting or treating angiogenesis (see abstract). Consequently, Willoughby does not teach away. It should be noted that a reference is not limited to its working examples, but must be evaluated for what it teaches those of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 U.S.P.Q. 507 (C.C.P.A. 1966). In re Chapman, 357 F.2d 418, 148 U.S.P.Q. 711 (C.C.P.A. 1966).

The applicant argues that *Willoughby et al.* teach reducing angiogenesis by reducing a granulation tissue, whereas, the non-woven tissues of HA benzyl esters have the opposite activity of inducing the formation of a granulation tissue, so again one skilled in the art would not be led to use HA benzyl ester for the purpose of the present invention. However, Willoughby et al. disclose the use of hyaluronic acid, including hyaluronic acid esters for the treatment of tumors by inhibiting or regressing angiogenesis (see claims 48-58; see also claims 24-34). Furthermore, Willoughby et al. disclose that their invention provides a process for the inhibition, control and/or regression of angiogenesis, (for example the inhibition of blood vessel growth to a malignant tumour, cutting off blood vessel growth or development, in to a malignant tumour) in a mammal (for example a human), the process comprising the steps of administering an effective dosage amount of a pharmaceutical composition for the inhibition, control and/or regression of angiogenesis to a site on/in the mammal in need of inhibition, control and/or regression ….. (see page 7, lines 6-32; see also page 6, lines 13-21).

The applicant argues that *Willoughby et al.* teach only the administration of compositions either topically or systemically, and do not suggest the application of biomaterials to the tumor site, as in the present invention. However, Willoughby et al. disclose the use of hyaluronic acid, including hyaluronic acid esters for the treatment of tumors by inhibiting or regressing angiogenesis (see claims 48-58; see also claims 24-34). Furthermore, Willoughby et al. disclose that their invention provides a process for the inhibition, control and/or regression of angiogenesis, (for example the inhibition of blood vessel growth to a malignant tumour, cutting off blood vessel growth or development, in to a malignant tumour) in a mammal (for example a human), the process comprising the steps of administering an effective dosage amount of a pharmaceutical composition for the inhibition, control and/or regression of angiogenesis to a site on/in the mammal in need of inhibition, control and/or regression ..... (see page 7, lines 6-32; see also page 6, lines 13-21). It should be noted that Willoughby teaching of administering the said hyaluronic acid to inhibit or treat angiogenesis of said tumors encompasses applying the said hyaluronic acid to said tumors as well as any of the common routes of administration. It should be noted that the use of different routes of administration of active ingredients or compositions such as Willoughby et al.'s is common in the art, is well within the purview of a skilled artisan and also depends on factors such as the type and/or severity of the tumor, disease or disorders and the type, weight and age of individual treated.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
january 4, 2009.

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